**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

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| **APPLICANT: MacLeod, C.L.** | § | **ART UNIT: 1635** |
| | § | |
| **FILED: January 27, 1999** | § | |
| | § | **EXAMINER: A. Wang** |
| **SERIAL NO.: 09/238,972** | § | |
| | § | |
| **FOR: Inhibition of Cationic Amino Acid Transporter and Uses Thereof** | § | **DOCKET: D5232CIP3** |

The Assistant Commissioner of Patents and Trademarks
**BOX AF**
Washington, DC 20231

**ATTENTION: Board of Patent Appeals and Interferences**

**TRANSMITTAL OF APPEAL BRIEF**

Dear Sir:

Enclosed please find three originals of the Appeal Brief for the above-referenced patent application.

This application was submitted on behalf of a small entity. A verified Statement of Small Entity Status was included with the patent application. A check in the amount of $205 is enclosed to cover the fee required for the Appeal Brief ($150) and the required 1 month extension fee ($55). If any additional fee is required, the Commissioner is hereby authorized to debit Account No. 07-1185.

Respectfully submitted,

Date: Jan 25, 2000

Benjamin Aaron Adler, Ph.D., J.D.
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AF/1641/635/8

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**Washington, DC 20231**

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**CERTIFICATE OF MAILING UNDER 37 CFR 1.8**

Dear Sir:

I hereby certify under 37 CFR 1.8 that the following correspondence is being deposited with the United States Postal Service as first class mail with sufficient postage on the date indicated below and is addressed to Commissioner of Patents and Trademarks, Washington DC 20231.

1) Transmittal letter for Appeal Brief;
2) Three copies of the Appeal Brief (17 pages) with two appendices (Claims on Appeal and References Cited);
3) Petition for Extension of Time (1 Month); and,
4) Check ($205) and return postcard.

Please return the enclosed postcard acknowledging receipt of this correspondence.

Respectfully submitted,

Date: Jan 25, 2000

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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The Assistant Commissioner of Patents and Trademarks
**BOX AF**
Washington, DC 20231

**ATTENTION: Board of Patent Appeals and Interferences**

# APPELLANT'S BRIEF

This Brief is in furtherance of the Notice of Appeal filed in this case on November 12, 1999. The fees required under 37 C.F.R. §1.17(f) and any other required fees are dealt with in the accompanying TRANSMITTAL OF APPEAL BRIEF.

In accordance with 37 C.F.R. §1.192(a), this Brief is submitted in triplicate.

# INDEX OF SUBJECT MATTER

## I. REAL PARTY IN INTEREST

The real party in interest is the Research Development Foundation.

## II. STATUS OF THE CLAIMS

Originally, claims 1-20 were filed with this Application. Claims 10-15 and 18-20 were withdrawn in response to the Restriction Requirement in the office action of April 13, 1999. Pending claims 1-9 and 16-17 are being appealed, of which claims 1,3, and 16 are independent claim.

## III. STATUS OF AMENDMENTS

Claims 1-9 and 16-17 were selected in response to the Restriction Requirement in the Office Action of April 13, 1999. No Amendments have been made to these claims. All pending claims are shown in Appendix A.

## IV. STATEMENT OF RELATED APPEALS AND INTERFERENCES

To Appellant's knowledge, there are no pending related appeals or interferences which will directly affect or be directly affected by the present appeal.

## V. SUMMARY OF THE INVENTION

The instant invention delineates the involvement of the CAT2 gene in L-arginine transport and nitric oxide synthesis in various cell types and pathological conditions (page 9, lines 5-8). The present invention describes how antisense oligonucleotides can be employed to prevent cationic amino acid transport, which in turn blocks production of nitric oxide in cells such as activated macrophages or cancer cells (page 27, lines 15-18). One object of the present invention is to provide an antisense methodology for inhibiting cationic amino acid transport comprising the step of administering to a human or a non-human mammal an effective dose of the antisense oligonucleotides of the present invention (Page 9, lines 13-17). Thus, the present invention provides an antisense

oligonucleotide directed against CAT2 mRNA (page 9, lines 17-18). A representative antisense oligonucleotide has the nucleotide sequence: GTAGGCTGAAACCCTGTCCTTGC (SEQ ID No. 2) (page 9, lines 18-20). Further, the present invention provides a pharmaceutical composition comprising the antisense oligonucleotide directed against CAT2 mRNA and a physiologically acceptable carrier (page 9, line 20 and page 10, lines 1-3). Generally, the methods of treating a pathophysiological state of the present invention may be useful for any disease characterized by an undesirable level of nitric oxide production (Page 28, lines 16-18). Preferably, this method will treat diseases selected from the group consisting of sepsis, cachexia, neoplastic diseases such as Kaposi's sarcoma, cerebral malaria, capillary leak syndrome and autoimmune disease (page 28, lines 19-20 and page 29, lines 1-2).

## VI. ISSUES

A. The 35 U.S.C. §102 Rejection

(1) Whether claims 3, 16, and 17 are anticipated by U.S. Patent No. **5,312,733** (**MacLeod**) under 35 USC §102(b).

B. The 35 USC §112 Rejections

(1) Whether claims 3 and 16 are not enabled under 35 USC §112, first paragraph, as "containing subject matter which was not described in the specification in such a way as convey to one skilled in the art that the inventor . . . had possession of the claimed invention."

(2) Whether claims 1-9 and 16 are not enabled under 35 USC §112, first paragraph.

## VII. GROUPING OF CLAIMS

The rejected claims do not stand or fall together. The Appellant considers claims 1-9 and 16-17 to lie in three embodiments of the present invention. Claims 1-2 are drawn to a method of inhibiting cationic amino acid transport by administering an effective dose of an antisense oligonucleotide directed against CAT2 mRNA. Claims 3-9 are drawn to a pharmaceutical composition comprising an antisense oligonucleotide directed against CAT2 mRNA and to the use of the pharmaceutical composition to inhibit nitric oxide production in

an individual for the treatment of disease. Claims 16-17 are directed to an antisense oligonucleotide directed against CAT2 mRNA.

## VIII. ARGUMENTS

### A. The 35 U.S.C. §102 Rejection

(1) Claims 3, 16, and 17 stand rejected under 35 USC §102(b) as being anticipated by U.S. Patent No. **5,312,733 (MacLeod)**. The current application is a continuation in part patent application of U.S. Patent Application Ser. No. 08/187,634, now **U.S. Patent 5,866,123** which is a continuation in part patent application of U.S. Patent Application Ser. No. 07/686,322, now **U.S. Patent 5,312,733** which is a continuation in part patent application of U.S. Patent Application Ser No. 07/509,684, now abandoned. Thus, the instant application is a continuation in part patent application of the patent application that resulted in U.S. Patent **5,312,733**.

The Examiner argues that legal priority regarding antisense oligonucleotides cannot be extended to U.S. Patent Application Ser. No. 07/686,322, now **U.S. Patent 5,312,733** because **U.S. Patent 5,312,733** describes the possibility of directing

antisense oligonucleotides against the sequences of the instant invention while intervening U.S. Patent Application Ser. No. 08/187,634 does not. Having denied the current application the benefit of the priority of application 08/686,322 (**U.S. Patent 5,312,733**) the Examiner then cites **U.S. Patent 5,312,733** as anticipating claims 3, 16, and 17 of the instant invention under 35 USC §102(b). This rejection is respectfully traversed.

The Examiner argues that 08/187,634, fails to incorporate the contents of 08/686,322 by reference "thereby preventing priority status to the filing date of application 08/686,322." The Appellant respectfully disagrees. The rules for referencing prior applications [37 CFR 178 (2)] state:

> Any nonprovisional application claiming the benefit of one or more prior filed copending applications... must contain... in the first sentence of the specification following the title a reference to each such prior application, identifying it by application number... and indicating the relationship of the applications.

This requirement was fulfilled by the first paragraph of 08/187,634 (Column 1 of **U.S. Patent 5,866,123** is the) under the heading "Cross Reference to Related Applications" which states:

> This application is a continuation-in-part of U.S. patent application Ser. No. 07/686,322, filed April 21, 1991, now U.S. Patent **5,312,733**, which is a continuation in part of U.S. patent application Ser No. 07/509,684, filed April 13, 1990, now abandoned

This reference has been placed in the first line of the specification of 08/187,634, now **U.S. Patent 5,866,123**, and thus satisfies this requirement. Based on this reference, the Appellant asserts that 08/187,634, now **U.S. Patent 5,866,123**, does indeed satisfactorily incorporate the contents of 08/686,322 by reference. Similarly, in the instant application, the requirement is satisfied on page 1, lines 11-16:

> This application is a continuation-in-part of U.S. Patent Application No. 08/187,634, filed January 26, 1994, which is a continuation-in-part of U.S. Patent Application No. 07/686,322, filed April 11, 1991, now U.S. Patent No. **5,312,733**, which is a continuation-in-part of U.S. Patent Application No. 07/509,684, filed April 13, 1990, now abandoned.

Therefore, the instant application also properly incorporates by reference the earlier applications.

Statute 35 U.S.C §120 states:

> An application for patent for an invention disclosed in the manner provided by the first paragraph of section 112 of this title in an application previously filed in the United States, or as provided by section 363 of this title, which is filed by an inventor or inventors named in the previously filed application shall have the same effect, as to such invention, as though filed on the date of the prior application, if filed before the patenting or abandonment of or termination of proceedings on the first application or on an application similarly entitled to the benefit of the filing date of the first application and if it contains or is

amended to contain a specific reference to the earlier filed application. (emphasis added)

In addition, Section 201.11 of the Manual of Patent Examining Procedure states under "Copendency" that "the first application may contain more that the second application, or the second may contain more that the first, and in either case the second application is entitled to the benefit of the first as to the common subject matter. It is not required that an intervening application must contain literally all of the contents of the first application(s) in order that a later application be entitled to the benefit of those contents.

While U.S. Patent Application Ser. No. 08/187,634 does not discuss antisense oligonucleotides directed against CAT2 mRNA, U.S. Patent Application Ser. No. 08/187,634 does disclose the gene sequence of CAT2. Given the disclosure of the sequence, the design and selection of an antisense oligonucleotide against CAT2 mRNA was completely within range of one with ordinary skill in the art. Thus, the specification of U.S. Patent Application Ser. No. 08/187,634 inherently provides the basis for support for antisense oligonucleotides directed against CAT2 mRNA since the specification discloses the gene sequence of CAT2.

The Appellant respectfully requests that the decision of the Examiner should be reversed, and priority of the instant invention to U.S. Patent application 07/686,322, now U.S. Patent **5,312,733** and to U.S. Patent Application Ser. No. 07/509,684 be restored. Furthermore, the Appellant respectfully requests that based on this priority, the Examiner's rejection of claims 3, 16, and 17 as anticipated by U.S. Patent No. **5,312,733** under 35 USC §102(b) be withdrawn and that claims 3, 16, and 17 be allowed.

B. The 35 USC §112 Rejections

(1) Claims 3 and 16 stand rejected under 35 USC §112, first paragraph, as "containing subject matter which was not described in the specification in such a way as convey to one skilled in the art that the inventor . . . had possession of the claimed invention." Specifically, the Examiner contends that the specification does not enable the formation of other inhibitory antisense oligonucleotides. The Appellant disagrees and this rejection is respectfully traversed.

It is relatively easy for those skilled in the art to design antisense sequences that effectively inhibit the expression of a gene. While the current application does not list the entire open reading frame of *CAT2*, the current application is a continuation-in-part of

application 08/187,634, now **U.S. Patent 5,866,123** which does list the entire sequence of the *CAT2* open reading frame. This sequence is also given in **MacLeod** et al. Mol. Cell. Biol., 10:3663-3674 (1990) and is also available from GenBank as accession no. M32485.

From the CAT2 open reading frame sequence provided, it would be easy for one skilled in the art to design additional oligonucleotides which would inhibit CAT2 expression. While not every oligonucleotide derived from a DNA sequence will function as desired, numerous predictive computer programs are available to determine which oligonucleotides which will preferentially associate with the desired target sequences rather than themselves or exogenous sequences. The most effective regions to target in a gene (e.g. the 5' end of the open reading frame) are well known to those skilled in the art. While the new oligonucleotides would need to be screened for effectiveness in inhibiting CAT2 expression, this would not constitute undue experimentation. With a small amount of screening, one skilled in the art could easily design other effective antisense oligonucleotides.

Since it is relatively easy for those skilled in the art to design antisense oligonucleotides to inhibit the expression of a given gene, it is less the design of the oligonucleotide and more the effect of

the resulting inhibition of the *CAT2* gene that is important in the instant invention. The Appellant has shown clearly that overexpression of the *CAT2* gene in Xenopus oocytes could be normalized with the antisense oligonucleotide. The Examiner argues that the specification does not provide any guidance regarding administration of "any type antisense oligo targeted to the *CAT2* gene that would result in an ameliorative effect of any particular pathological state . . . [or] pathological condition by inhibiting CAT2." However, the result described in the specification show that the antisense oligonucleotide is capable of alleviating overexpression of the *CAT2* gene *in vitro*.

CAT2 regulates intracellular arginine accumulation. As nitric oxide is the sole precursor for nitric oxide synthesis, limitation of arginine transport will also result in an inhibition of nitric oxide production. Numerous diseases are known to have elevated nitric oxide levels as described on pages 4-8 of the specification. For example, nitric oxide is elevated in breast cancer and the degree of elevation correlates with the grade of the tumor (page 4, lines 5-8 of the specification). Therefore, it is highly likely that the instant invention would be efficacious in the treatment of breast cancer.

For the reasons given above, the Appellant respectfully requests that the decision of the Examiner should be reversed, and that claims 3 and 16 be allowed.

(2) Claims 1-9 and 16 stand rejected under 35 USC §112, first paragraph. The Examiner argues that the specification is "only enabling for claims limited to an antisense oligo consisting of SEQ ID No: 2 and a method of inhibiting CAT2 expression using said antisense oligonucleotide." The Examiner also contends that no specific guidance is provided for application of the instant invention to any particular disease condition. This rejection is respectfully traversed.

The issue of whether one skilled in the art could easily design additional inhibitory antisense oligonucleotides has been discussed above. The Appellant again asserts that it would be relatively easy for those skilled in the art to design additional antisense oligonucleotides from the sequence of the *CAT2* cDNA as given in **U.S. Patent 5,866,123**; **MacLeod** *et al.* Mol. Cell. Biol., 10:3663-3674 (1990); and GenBank accession no. M32485. The Appellant reiterates that there are numerous predictive computer programs available to help eliminate inherently troublesome oligonucleotides. The Examiner has disputed that the 55% success rate

of **Hoke** *et al.*, (U.S. Patent 5,585,479; previously made of record) in designing effective antisense oligonucleotides against human ELAM-I mRNA is significant to the instant invention. In **Hoke** *et al.*, 22 antisense oligonucleotides were designed. Of these 22, 12 (55%) oligonucleotides were successful enough in inhibiting ELAM-I to recited in the claims of U.S. Patent 5,585,479.

The mechanisms by which the various nuclear genes are transcribed and translated are essentially identical. Thus, it would be logical that the mechanisms of inhibiting these processes from gene to gene would also be identical. Thus, the Appellant respectfully reasserts that the 55% success rate of **Hoke** et al. does suggest a similar rate of success for the instant invention as well. At such a rate of success, the necessary screening of the oligonucleotides for effectiveness would not constitute undue experimentation. With a small amount of screening, one skilled in the art could easily design other effective antisense oligonucleotides.

The Appellant has clearly shown that overexpression of the *CAT2* gene in Xenopus oocytes could be normalized with an antisense oligonucleotide. This shows that a least part of the gene is physically available for antisense inhibition. As such, there is no compelling reason why it should be any more difficult to design

additional antisense oligonucleotides for the *CAT2* gene than it was for **Hoke** *et al.* to design them for *ELAM-1* RNA. While some transcripts may be folded such that it is impossible for an antisense molecule to access the transcript, the success of the oligonucleotide designed by the Applicant shows that this is not the case for the *CAT2* gene. There is no scientific proof that the design of additional antisense oligonucleotides for the *CAT2* gene would be so difficult as to rise to the level of "undue experimentation" under 35 USC §112, first paragraph.

The Examiner also argues that the specification does not provide any guidance regarding administration of "any type antisense oligo targeted to CAT2 that would result in an ameliorative effect of any particular pathological state . . . [or] pathological condition by inhibiting CAT2." The Examiner argued (Office Action of April 13, 1999) that the clinical application of antisense is questioned since there are several obstacles that must be overcome such as degradation, molecular size and charge, bioavailability, and toxicity. As delivery methods improve, so will the efficiency of antisense therapy. The present invention demonstrates that antisense inhibition of the *CAT2* gene can restore arginine transport to normal levels and thus affect nitric oxide production.

Even though no specific instance of *in vivo* ameliorative effects is given in the specification, it cannot be disputed that the instant invention is useful in downregulating arginine transport and thus nitric oxide production. Since nitric oxide is such an important regulatory molecule, there can be no doubt that the instant application will have ameliorative effects *in vivo*.

In light of the arguments above, the Appellant maintains that the invention is in fact enabled. As such, the Appellant respectfully requests that the decision of the Examiner should be reversed, and that claims 1-9 and 16 be allowed.

Respectfully submitted,

Date: Jan 24, 2000

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## CLAIMS ON APPEAL

**WHAT IS CLAIMED IS:**

1. A method of inhibiting cationic amino acid transport comprising the step of administering to a human or a non-human mammal an effective dose of an antisense oligonucleotide directed against CAT2 mRNA.

2. The method of claim 1, wherein said antisense oligonucleotide has the nucleotide sequence: GTAGGCTGAAACCCTGTCCTTGC (SEQ ID No. 2).

3. A pharmaceutical composition comprising an antisense oligonucleotide directed against CAT2 mRNA and a physiologically acceptable carrier.

4. A method of inhibiting the production of nitric oxide in an individual in need of such treatment comprising the step of administering to said individual an effective dose of the pharmaceutical composition of claim 3.

5. A method of treating a pathophysiological state in an individual wherein said state is characterized by production of an undesirable level of nitric oxide, comprising the step of administering to said individual an effective dose of the pharmaceutical composition of claim 3.

6. The method of claim 5, wherein said pathophysiological state is selected from the group consisting of sepsis, neoplastic disease, autoimmune diseases, cachexia, cerebral malaria, cardiovascular disease, cerebrovascular disease and capillary leak syndrome.

7. The method of claim 6, wherein said autoimmune disease is selected from the group consisting of systemic lupus erythematosus, rheumatoid arthritis and multiple sclerosis.

8. The method of claim 6 wherein said neoplastic disease is selected from the group consisting of breast cancer and lung cancer.

9. A method of treating breast cancer in an individual in need of such treatment, comprising the step of administering to said individual an effective dose of the pharmaceutical composition of claim 3.

16. An antisense oligonucleotide directed against CAT2 mRNA.

17. The antisense oligonucleotide of claim 16, wherein said antisense oligonucleotide has the nucleotide sequence: GTAGGCTGAAACCCTGTCCTTGC (SEQ ID No. 2).